

AMENDMENT AND RESPONSE TO OFFICE ACTION

(SEQ ID NO:6), DSVVYGLRSK (SEQ ID NO:7), LDSAS (SEQ ID NO:8), SDV [(SEQ ID NO:9)], PNGRGESLAY (SEQ ID NO:11), and DRYLKFRPV (SEQ ID NO:12).

15. (Amended) The method of claim 1, wherein the target cell is a neutrophil or a [myofiboblast] myofibroblast.

24. (Amended) The adhesion modulatory peptide of claim 20, comprising an amino acid residue sequence selected from the group consisting of DDDRKWGFC (SEQ ID NO:6), DSVVYGLRSK (SEQ ID NO:7), LDSAS (SEQ ID NO:8), SDV [(SEQ ID NO:9)], PNGRGESLAY (SEQ ID NO:11), and DRYLKFRPV (SEQ ID NO:12).

Remarks

Claims 1-29 are pending. Claims 1 and 15 have been amended. Support for claim 1 can be found, for example, at page 3, lines 1-2; page 2, lines 25-29; and page 4, lines 1-9. Support for the amendment to claim 2 can be found, for example, at page 3, line 1. Amendments to claims 7, 8, 9, and 24, were made to correct grammatical errors and provide proper antecedent basis.

The claimed methods are directed to enhancing or decreasing adhesion *via* the enhancement or disruption of specific target cells or cell types adhering to a substrate *based on the adhesion receptors expressed by the specific cell or cell type*. As will be described below, the peptides are structurally defined by the receptors to which they interact. The peptides of the present invention *are predicated on the known structural features of ligand binding motifs of known integrin/receptors* (i.e. those that have been well characterized in the art). The integrin binding pocket is comprised of known amino acid residues from both of the alpha and beta

AMENDMENT AND RESPONSE TO OFFICE ACTION

subunits. It is these amino acids that confine and define the structure of the pocket and therefore the structure of ligand(s).

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 1, 3-5, 7, 8, 11-13, and 15-19 were rejected under 35 U.S.C. § 112, first paragraph, as not being enabled. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The examiner asserts that "there is insufficient direction or objective evidence as to how to make and how to use any peptide, which inhibits any adhesion activity *for the number of possibilities associated with the myriad of indirect effects associated with various adhesion pathways*" (emphasis added). The claims are directed to enhancing or decreasing adhesion *via the enhancement or disruption of specific target cells or cell types adhering to a substrate based on the adhesion receptors expressed by the specific cell or cell type* (see page 2, lines 25-31). The applicant respectfully requests clarification as to how a "myriad of indirect effects", associated with adhesion *pathways*, has any bearing on issues related to an enabling disclosure for claims directed to extracellular interactions (for example, between receptors and receptors, and receptors and ligands).

One of ordinary skill in the art will recognize that the structure of a peptide/ligand is defined by the receptor to which it interacts (i.e. the receptor/cell binding motif of each peptide provides the proper structure recognized by specific receptors/cell surface molecules). As stated in the Summary of the Invention, "there exists a need for peptides *having an amino acid structure that provides the optimum specificity for the receptor of interest*" (emphasis added).

AMENDMENT AND RESPONSE TO OFFICE ACTION

The claimed peptides have particular utility in promoting cell retention and spreading and/or inhibiting cellular attachment, which may have a *subsequent* effect on cellular apoptosis and supporting tissue growth. One of ordinary skill in the art will immediately recognize that such functions are readily observed, or screened for, by mere observation. One of ordinary skill in the art regularly determines cell types (and phenotypes of cellular species), cellular growth and spread (or lack thereof), cell retention, and apoptosis *via* microscopic observation.

The Examiner points to a reference by Kogan *et al.* (J. Biol. Chem., 1995) in order to provide basis for his enablement rejection. Kogan uses methods well defined in the art to ascertain the proper configuration of the E-selectin molecule binding to sLe^x. What was undertaken by Kogan was an "wreck and check" analysis of a molecule that has already been shown to bind to sLe^x. Mutagenic analysis (i.e. "wrecking") and the subsequent assaying of binding (i.e. "checking"), was done to merely prove, or disprove, a proposed model of binding. Any person of ordinary skill in the art will readily recognize that mutagenic analysis is typically used to ascertain function (or in this case binding conformation) *via* a showing of which residues play important roles in governing overall molecule activity.

As the Kogan reference suggests, it is well established that the one of the most common ways in which new molecules are designed involves the use of *known targets as starting points*. Well characterized targets allow for the proposed ligands to be evaluated in the binding site prior to synthesis. Indeed the most potent inhibitors, or enhancers, of receptor mediated function are based on such concepts. This is very much state-of-the-art in pharmaceutical design involving a medicinal chemist designing peptides based on what is perceived to be an optimal substrate.

AMENDMENT AND RESPONSE TO OFFICE ACTION

In essence once a suitable receptor directed ligand is found, amino acid residues in the optimal substrate are deleted/substituted with other moieties to find the optimal inhibitor (depending upon project goal(s)). This uses both molecular modeling and structure determination (X-ray/NMR). *Much of the literature that claims to use **structure-based drug design** methods, model a candidate drug by placing it into the active site using a previously determined structure.* The part of the drug that interacts with the receptor "core" is used to position the ligand. The other groups are then built in manually (using well-known computer graphics). An evaluation of the quality of the candidate usually includes steric fit, hydrophobic and hydrogen bond interactions, and/or a highly favorable molecular mechanics energy (inter and intramolecular ligand energy), all of which can be determined by one of ordinary skill in the art. Suitable likely candidates are thus identified. These compounds are then tested for (1) binding affinity and if this proves promising, for (2) bioavailability and, again if this proves promising, (3) a structure would be determined (after all, as stated on page 2, lines 4-6 of the specification, "there exists a need for peptides having an amino acid structure that provides the optimum specificity for the receptor of interest"). Successive rounds of such optimization allows one of ordinary skill to combine the characteristics of high affinity (as measured, for example, by IC50) and bioavailability (in animal tests). It should be noted that robust methods of lead modification have been, and continue to be, the mainstay of modern structure-based drug design. If anything, the Kogan reference is an example of such methods that are commonly available to one of ordinary skill in the art (the Examiner is respectfully reminded that it has been well-established that the applicant need not provide, in the specification, those methods, assays and reagents that

AMENDMENT AND RESPONSE TO OFFICE ACTION

are commonly used and well-known in the art). Such experimentation would not be considered to be "undue".

In view of the foregoing, the applicant submits that the receptor(s) of interest define the claimed peptides, both structurally and functionally. It is well known that receptors retain specificity *via* their ligand binding domains. Some integrins bind only one matrix molecule such as fibronectin or laminin, others bind more than one: an integrin that is present on fibroblasts, for example, binds collagen, fibronectin, and laminin. One subfamily of integrins recognizes the RGD sequence present in these and other matrix proteins, while other integrins recognize various other sequences. One of ordinary skill in the art will recognize that many studies have been undertaken to identify domain(s) within integrin subunits that confer binding specificity. Several lines of evidence have shown that the integrin ligand binding pocket is comprised of amino acid residues on both the alpha and beta subunits of the integrin. Based upon these types of studies, it is well established in the art that the integrin ligand binding motifs, and the amino acids therein, have been significantly characterized and the general location of the ligand binding site has been generally mapped. These well-characterized extracellular binding motifs, and the amino acids that are at the core of forming each unique motif, provide for a "lock" that is can only be accessed by a ligand of proper structure (i.e. a "key"). This analogy to a "lock and key" is an important one. If one can conceptualize the role of the predetermined and defined target receptor/integrin in demanding a specific structure of the compound that increases or decreases cell adhesion, then one will realize that the compound structure is clearly defined. The "target" receptor/integrin is defined by those interactions and forces present in the ligand binding motif,

AMENDMENT AND RESPONSE TO OFFICE ACTION

as described in the specification. Given a knowledge of the receptor specificity, as presented for many receptors in the specification (see, for example, pages 19 and 20, and Table II), one of ordinary skill could ascertain and obtain peptide-associated substrates, wherein the peptides are useful ligands (i.e. harboring proper structure to interact with ligand binding motif of "target" cellular receptor/integrin). The examiner asserts that since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a peptide's amino acid sequence and still retain similar biological activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved. The applicant submits that the peptides of the present invention *are predicated on the known structural features of ligand binding motifs of known integrin/receptors* (i.e. those that have been well characterized in the art). The integrin binding pocket is comprised of known amino acid residues from both of the alpha and beta subunits. It is these amino acids that confine and define the structure of the pocket and therefore the structure of ligand(s).

Claims 1, 3-5, 7, 8, 11-13, and 15-19 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

AMENDMENT AND RESPONSE TO OFFICE ACTION

The standard regarding what is or is not supported by the specification has been clearly articulated as "requiring the specification to convey with reasonable clarity to those skilled in the art that, as of the filing date sought, the inventor was in possession of the invention", i.e., whatever is now claimed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). Compliance with the written description requirement is essentially a fact-based inquiry that will "necessarily vary depending on the nature of the invention claimed." *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991) (citing *In re DiLeone*, 436 F.2d 1404, 1405 (CCPA 1971)). Satisfaction of the written description requirement is determined on a case-by-case basis.

The inquiry into whether or not there is an adequate written description is not performed in a vacuum. "Knowledge of one skilled in the art is relevant to meeting [the written description] requirement." *Enzo Biochem, Inc. v. Gen-Probe*, Docket No. 01-1230 (Fed. Cir. Apr. 2, 2002) (slip op.). This fact has implications not only for validity challenges, but also for patent prosecution. See *In re Alton*, 76 F.3d 1168, 1174-75 (Fed. Cir. 1996).

In the most recent CAFC decision, *Enzo Biochem, Inc. v. Gen-Probe*, Docket No. 01-1230 (Fed. Cir. July 15, 2002), the Federal Circuit vacated a prior decision, *Enzo Biochem, Inc. v. Gen-Probe*, 285 F.3d 1013, 62 USPQ 2d 1289 (Fed. Cir. April 2, 2002), and reversed the district court's grant of summary judgment that Enzo's claims are invalid for failure to meet the written description requirement, stating in relevant part:

"It is not correct, however, that all functional descriptions of genetic material fail to meet the written description requirement. The PTO has issued Guidelines governing its internal

AMENDMENT AND RESPONSE TO OFFICE ACTION

practice for addressing that issue. The Guidelines, like the Manual of Patent Examining Procedure ("MPEP"), are not binding on this court, but may be given judicial notice to the extent they do not conflict with the statute. See Molins PLC v. Textron, Inc., 48 F.3d 1172, 1180 n.10, 33 USPQ2d 1823, 1828 n.10 (Fed. Cir. 1995). In its Guidelines, the PTO has determined that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . *i.e.*, complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Guidelines, 66 Fed. Reg. at 1106 (emphasis added). For example, the PTO would find compliance with § 112, ¶ 1, for a claim to an "isolated antibody capable of binding to antigen X," notwithstanding the functional definition of the antibody, in light of "the art-recognized method of making antibodies *to fully characterized antigens*, the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that the *antibody technology is well developed and mature*." (emphasis added) Synopsis of Application of Written Description Guidelines, at 60, available at <http://www.uspto.gov/web/patents/guides.htm> ("Application of Guidelines"). With reference to the claimed nucleotide sequences of Enzo, the Board also noted that "[B]ecause the claimed nucleotide sequences preferentially bind to the genomic DNA of the deposited strains of *N. gonorrhoeae* and have a complementary structural relationship with that DNA, those sequences, under the PTO Guidelines, may also be adequately described. . . . [A]lthough the patent specification lacks description of the location along the bacterial DNA to which the claimed

AMENDMENT AND RESPONSE TO OFFICE ACTION

sequences bind, Enzo has at least raised a genuine issue of material fact as to whether a reasonable fact-finder could conclude that *the claimed sequences are described by their ability to hybridize to structures that, while not explicitly sequenced, are accessible to the public.*"

The PTO Guidelines clearly state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. Guidelines, 66 Fed. at 1106." (emphasis added) *Enzo Biochem, Inc. v. Gen-Probe*, Docket No. 01-1230 (Fed. Cir. July 15, 2002).

The Examiner has stated that a "skilled artisan cannot envision all the contemplated peptide sequence possibilities recited in the instant claims." The applicant respectfully submits that in view of the receptors of claim 1, the structural and functional properties of the claimed peptides are characterized. This characterization is a direct benefit from analysis of receptor binding ligand domains from well known and well characterized receptors/integrins. Therefore, the claims, as amended, no longer encompass "any adhesion modulatory peptide". As discussed in the foregoing section, the peptides of the present invention *are predicated on the known structural features of ligand binding motifs of known integrin/receptors* (i.e. those that have been well characterized in the art). The integrin binding pocket is comprised of known amino acid residues from both of the alpha and beta subunits. It is these amino acids that confine and define the structure of the pocket and therefore the structure of ligand(s).

AMENDMENT AND RESPONSE TO OFFICE ACTION

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 1, 4, 5, 7, 8, 11-13, and 15-19 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Claim 1 was rejected for being indefinite in its recitation of the term "modulating" because it was asserted to be ambiguous as to the direction or degree of modulation. The applicant has amended claim 1 to provide direction to the adhesion of a target cell to a substrate.

Rejection Under 35 U.S.C. § 102

Claims 1, 4, 5, 12, 13, 16, 18 and 19 were rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,330,911 to Hubbell *et al.* ("Hubbell"). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Hubbell teaches the inhibition of cell spreading on RGD and YIGSR peptide-grafted surfaces due to the presence of soluble peptide in the surrounding medium. Hubbell does not teach or contemplate a peptide whose structure is inherently predicated on the binding motifs of $\alpha 4 \beta 1$ integrins and/or VCAM receptors expressed on/by the target cell.

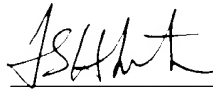
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AMENDMENT AND RESPONSE TO OFFICE ACTION

Allowance of claims 1-29 is respectfully solicited.

Respectfully submitted,



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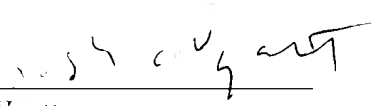
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AMENDMENT AND RESPONSE TO OFFICE ACTION

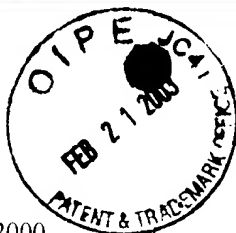
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Aisha Wyatt

Date: February 18, 2003



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MARKED UP VERSION OF AMENDMENTS PURSUANT TO 37 C.F.R. § 1.121

Marked Up Version of Amended Claims

Pursuant to 37 C.F.R. § 1.121(c)(1)(ii)

1. (Amended) A method [of modulating] for enhancing or decreasing adhesion of a target cell to a substrate, comprising providing the target cell with an adhesion modulatory peptide-associated substrate such that adhesion of the target cell to the substrate is [modulated] enhanced or decreased as compared to substrate alone, wherein the target cell expresses a receptor selected from the group consisting of $\alpha 4 \beta 1$ integrins and VCAMs, wherein the peptide binds to the receptors.
2. (Amended) The method of claim 1, wherein the adhesion modulatory peptide comprises a peptide which specifically [enhances] stimulates adhesion of the target cell.
3. The method of claim 1, wherein the adhesion modulatory peptide comprises a peptide which specifically inhibits adhesion of the target cell.
4. The method of claim 1, wherein the adhesion modulatory peptide is selected from the group consisting of an endothelial cell adhesion modulatory peptide, a fibroblast adhesion modulatory peptide and a macrophage adhesion modulatory peptide.
5. The method of claim 4, wherein the adhesion modulatory peptide is an endothelial cell adhesion modulatory peptide.
6. The method of claim 4, wherein the adhesion modulatory peptide is a fibroblast adhesion modulatory peptide.

7. (Amended) The method of claim 4, wherein the adhesion modulatory peptide is a [neotrophil] neutrophil adhesion modulatory peptide or a myofibroblast adhesion modulatory peptide.

8. (Amended) The method of claim 1, wherein the adhesion modulatory peptide comprises an amino acid residue sequence selected from the group consisting of SDQDNNGKGSHEs (SEQ ID NO:1), SDQDQDGDGHQDS (SEQ ID NO:2), GRGDNPS (SEQ ID NO:3), TPVVPTVDITYDGRGDSLAY (SEQ ID NO:4), TPVVPTVDITYDGRGD (SEQ ID NO:5), HDRKEFAKFEEERARA [(SEQ ID NO:10)] (SEQ ID NO:9), DPGYIGSR (SEQ ID NO:10), KGMNYTVR (SEQ ID NO:13), and VLEP (SEQ ID NO:15).

9. (Amended) The method of claim 1, wherein the adhesion modulatory peptide comprises an amino acid residue sequence selected from the group consisting of DDRKWGFC (SEQ ID NO:6), DSVVYGLRSK (SEQ ID NO:7), LDSAS (SEQ ID NO:8), SDV [(SEQ ID NO:9)], PNGRGESLAY (SEQ ID NO:11), and DRYLKFRPV (SEQ ID NO:12).

10. The method of claim 1, wherein the adhesion modulatory molecule enhances binding of an adhesion receptor predominantly expressed by the target cell.

11. The method of claim 1, wherein the adhesion modulatory molecule inhibits binding of an adhesion receptor predominantly expressed by the target cell.

12. The method of claim 1, wherein the target cell is selected from the group consisting of an endothelial cell, a fibroblast and a macrophage.

13. The method of claim 12, wherein the target cell is an endothelial cell.

14. The method of claim 12, wherein the target cell is a fibroblast.
15. The method of claim 1, wherein the target cell is a neutrophil or a myofibroblast.
16. The method of claim 1, wherein the target cell is within a cell population.
17. The method of claim 1, wherein the target cell is within a subject.
18. The method of claim 1, wherein the substrate is selected from the group consisting of a polyvinyl surface, a gel, collagen, hyaluronic acid, titanium and PGA.
19. The method of claim 1, further comprising contacting the substrate with the adhesion modulatory peptide, forming the adhesion modulatory peptide-associated substrate prior to providing the cell with the substrate.
20. An adhesion modulatory peptide which modulates adhesion of a target cell to a substrate.
21. The adhesion modulatory peptide of claim 20, wherein the peptide enhances adhesion of a target cell to a substrate.
22. The adhesion modulatory peptide of claim 20, wherein the peptide inhibits adhesion of a target cell to a substrate.
23. The adhesion modulatory peptide of claim 20, comprising an amino acid residue sequence selected from the group consisting of SDQDNNGKGSSES (SEQ ID NO:1), SDQDQDGDGHQDS (SEQ ID NO:2), GRGDNPS (SEQ ID NO:3), TPVVPTVDITYDGRGDSLAY (SEQ ID NO:4), TPVVPTVDITYDGRGD (SEQ ID NO:5),

HDRKEFAKFEEERARA (SEQ ID NO:9), DPGYIGSR (SEQ ID NO:10), KGMNYTVR (SEQ ID NO:13), and VLEP (SEQ ID NO:15).

24. (Amended) The adhesion modulatory peptide of claim 20, comprising an amino acid residue sequence selected from the group consisting of DDDRKWGFC (SEQ ID NO:6), DSVVYGLRSK (SEQ ID NO:7), LDSAS (SEQ ID NO:8), SDV [(SEQ ID NO:9)], PNGRGESLAY (SEQ ID NO:11), and DRYLKFRPV (SEQ ID NO:12).

25. The adhesion modulatory peptide of claim 20 having a molecular weight less than about 2500 Da.

26. A substrate treated with the adhesion modulatory peptide of claim 20.

27. A device treated with the adhesion modulatory peptide of claim 20.

28. A composition comprising the adhesion modulatory peptide of claim 20 and a carrier suitable for *in vivo* use.

29. A device for modulation of adhesion of a target cell comprising a substrate in combination with an adhesion-modulatory peptide, forming a device for modulating adhesion.

Clean Version of Amended Claims

Pursuant to 37 C.F.R. § 1.121(c)(1)(ii)

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1. (Amended) A method for enhancing or decreasing adhesion of a target cell to a substrate, comprising providing the target cell with an adhesion modulatory peptide-associated substrate such that adhesion of the target cell to the substrate is enhanced or decreased as compared to substrate alone, wherein the target cell expresses a receptor selected from the group consisting of $\alpha 4\beta 1$ integrins and VCAMs, wherein the peptide binds to the receptors.

2. (Amended) The method of claim 1, wherein the adhesion modulatory peptide comprises a peptide which specifically stimulates adhesion of the target cell.

3. The method of claim 1, wherein the adhesion modulatory peptide comprises a peptide which specifically inhibits adhesion of the target cell.

4. The method of claim 1, wherein the adhesion modulatory peptide is selected from the group consisting of an endothelial cell adhesion modulatory peptide, a fibroblast adhesion modulatory peptide and a macrophage adhesion modulatory peptide.

5. The method of claim 4, wherein the adhesion modulatory peptide is an endothelial cell adhesion modulatory peptide.

6. The method of claim 4, wherein the adhesion modulatory peptide is a fibroblast adhesion modulatory peptide.

A⁴
7. (Amended) The method of claim 4, wherein the adhesion modulatory peptide is a neutrophil adhesion modulatory peptide or a myofibroblast adhesion modulatory peptide.

8. (Amended) The method of claim 1, wherein the adhesion modulatory peptide comprises an amino acid residue sequence selected from the group consisting of SDQDNNGKGSHE (SEQ ID NO:1), SDQDQDGDGHQDS (SEQ ID NO:2), GRGDNPS (SEQ ID NO:3), TPVVPTVDITYDGRGDSLAY (SEQ ID NO:4), TPVVPTVDITYDGRGD (SEQ ID NO:5), HDRKEFAKFEEERARA (SEQ ID NO:9), DPGYIGSR (SEQ ID NO:10), KGMNYTVR (SEQ ID NO:13), and VLEP (SEQ ID NO:15).

9. (Amended) The method of claim 1, wherein the adhesion modulatory peptide comprises an amino acid residue sequence selected from the group consisting of DDDRKWGFC (SEQ ID NO:6), DSVVYGLRSK (SEQ ID NO:7), LDSAS (SEQ ID NO:8), SDV, PNGRGESLAY (SEQ ID NO:11), and DRYLKFRPV (SEQ ID NO:12).

10. The method of claim 1, wherein the adhesion modulatory molecule enhances binding of an adhesion receptor predominantly expressed by the target cell.

11. The method of claim 1, wherein the adhesion modulatory molecule inhibits binding of an adhesion receptor predominantly expressed by the target cell.

12. The method of claim 1, wherein the target cell is selected from the group consisting of an endothelial cell, a fibroblast and a macrophage.

13. The method of claim 12, wherein the target cell is an endothelial cell.

14. The method of claim 12, wherein the target cell is a fibroblast.

15. The method of claim 1, wherein the target cell is a neutrophil or a myofibroblast.

16. The method of claim 1, wherein the target cell is within a cell population.

17. The method of claim 1, wherein the target cell is within a subject.
18. The method of claim 1, wherein the substrate is selected from the group consisting of a polyvinyl surface, a gel, collagen, hyaluronic acid, titanium and PGA.
19. The method of claim 1, further comprising contacting the substrate with the adhesion modulatory peptide, forming the adhesion modulatory peptide-associated substrate prior to providing the cell with the substrate.
20. An adhesion modulatory peptide which modulates adhesion of a target cell to a substrate.
21. The adhesion modulatory peptide of claim 20, wherein the peptide enhances adhesion of a target cell to a substrate.
22. The adhesion modulatory peptide of claim 20, wherein the peptide inhibits adhesion of a target cell to a substrate.
23. The adhesion modulatory peptide of claim 20, comprising an amino acid residue sequence selected from the group consisting of SDQDNNGKGSSES (SEQ ID NO:1), SDQDQDGDGHQDS (SEQ ID NO:2), GRGDNPS (SEQ ID NO:3), TPVVPTVDITYDGRGDSLAY (SEQ ID NO:4), TPVVPTVDITYDGRGD (SEQ ID NO:5), HDRKEFAKFEEERARA (SEQ ID NO:9), DPGYIGSR (SEQ ID NO:10), KGMNYTVR (SEQ ID NO:13), and VLEP (SEQ ID NO:15).
24. (Amended) The adhesion modulatory peptide of claim 20, comprising an amino acid residue sequence selected from the group consisting of DDDRK WGFC (SEQ ID NO:6),

DSVVYGLRSK (SEQ ID NO:7), LDSAS (SEQ ID NO:8), SDV, PNGRGESLAY (SEQ ID NO:11), and DRYLKFRPV (SEQ ID NO:12).

25. The adhesion modulatory peptide of claim 20 having a molecular weight less than about 2500 Da.

26. A substrate treated with the adhesion modulatory peptide of claim 20.

27. A device treated with the adhesion modulatory peptide of claim 20.

28. A composition comprising the adhesion modulatory peptide of claim 20 and a carrier suitable for *in vivo* use.

29. A device for modulation of adhesion of a target cell comprising a substrate in combination with an adhesion-modulatory peptide, forming a device for modulating adhesion.



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MARKED UP VERSION OF AMENDMENTS PURSUANT TO 37 C.F.R. § 1.121

Marked Up Version of Amended Specification Paragraphs

Pursuant to 37 C.F.R. § 1.121(b)(1)(iii)

Please replace the paragraph on page 2, lines 7-19, with the following paragraph.

--The present invention satisfies this need and provides related advantages as well. In particular, the present invention features adhesion modulatory peptides which modulate the adhesion of specific cells or cell types based on the adhesion receptors expressed by the specific cell or cell type. The adhesion modulatory peptides are designed to promote and/or enhance the adhesion of specific cells or cell types based on the adhesion receptors expressed by the specific cell or cell type (e.g. the cells receptor expression profile). The present invention features a method of modulating (e.g. enhancing and/or inhibiting) adhesion of a target cell (e.g. endothelial cells, fibroblasts, macrophages, neutrophils and [myofibroblasts] myofibroblasts) to a substrate (e.g., polyvinyl surfaces, gels, collagen, hyaluronic acid, titanium and PGA) which includes providing the cell with an adhesion modulatory peptide-associated substrate such that adhesion of the target cell to the substrate is modulated. The target [cells] cells of the present invention can be present in a cell population and/or in a subject (e.g., a human subject). --

Please replace the paragraph on page 3, lines 20-31, with the following paragraph.

--The term "target cell includes" a cell (e.g., a mammalian cell) which is capable of binding or has the ability to bind to an adhesion-modulatory peptide or adhesion-modulatory peptide associated substrate of the present invention. In one embodiment, a target cell is present within a subject. In another embodiment, a target cell is isolated from a subject (e.g., a human

U.S.S.N. 09/732,411

Filed: November 7, 2000

MARKED UP VERSION OF AMENDMENTS PURSUANT TO 37 C.F.R. § 1.121

subject). In yet another embodiment, the target cell is present with a cell population. The term "cell population" includes a collection or group including the target cell and at least a second cell type. Cell populations can also include three, four, five, six, or more cell types or can include any number of cell types greater than one (e.g., the target cell and additional undefined cell types). Preferred target cells include, but are not limited to endothelial cells, fibroblasts and macrophages. Additional preferred target cells include, but are not limited to neutrophils and [myofibroblasts] myofibroblasts.--

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